Kidney International, Vol. 30 (1986), pp. 81–84

Phenacetin and papillary necrosis: Independent risk factors for renal pelvic cancer

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Phenacetin and papillary necrosis: independent risk factors for renal pelvic cancer. A case–control study was undertaken to determine whether renal papillary necrosis (RPN) is an essential step in the genesis of analgesic–associated cancer of the renal pelvis (CaP). Kidneys of 66 patients (and 86 cases of renal parenchymal cancer (CaK), for comparison) were examined for evidence of RPN. Information concerning past consumption of phenacetin–containing analgesics (PhA) was obtained from all cases and 751 population controls by means of a questionnaire. Separately, RPN and regular consumption of PhA each conferred a relative risk for CaP of 3-1/2 to 7, while together they increased the risk some 20 times that for non-consumers without RPN. This suggests that each factor has independent, and when they coexist sequential, effects. The risk for CaK was doubled by regular PhA consumption but was not increased by RPN.

Although renal papillary necrosis (RPN) has been found in a high proportion of subjects with analgesic–associated cancer of the renal pelvis (CaP), there is no agreement as to whether RPN is an essential step in the genesis of this cancer. Those who believe that phenacetin itself is a chemical carcinogen, generally have postulated that those tissue changes which precede transitional–cell carcinoma occur separately from, and parallel to, phenacetin's nephrotoxic effect which results in RPN [1]. Thus can be explained the production of urothelial tumors, apparently without co-existing RPN, by feeding phenacetin to rats [2], a species which is resistant to the nephrotoxic effects of this drug [3].

On the other hand, by analogy with transitional–cell tumors which arise in association with chronic urological disease, it has been proposed that RPN, which frequently is associated with urinary obstruction and infection, is an intermediate stage in the development of CaP. In support of this is the observation that in patients who have taken analgesics, CaP has been reported infrequently in the absence of RPN. Indeed, RPN has been found in 75% of the 124 well–documented case reports of analgesic–associated CaP published up to, and including, 1973 [4] and in 92, 87 and 57%, respectively, of one Swedish and two Australian series of such cases published between 1974 and 1979 [5–7].

To elucidate whether the presence of RPN is a necessary intermediate stage in the development of analgesic–associated CaP, a retrospective case–control study was undertaken to determine the relative risk associated with the presence of RPN alone, the consumption of phenacetin–containing analgesics (PhA) alone, or the occurrence of both risk factors together. Information was obtained from patients with CaP concerning their past consumption of analgesics, and the kidneys from these patients were examined for evidence of RPN. A comparison was made with patients with adenocarcinoma of the kidney (CaK).

Methods

All adult cases of primary kidney cancer admitted to five major teaching hospitals in Sydney between January 1977 and September 1982, and a sixth teaching hospital between January 1970 and September 1982 were included if surgical specimens were available for examination. One of two pathologists (JJC and JT) classified the tumors according to their histological appearances as arising from the renal pelvis (including both transitional–cell and squamous–cell carcinomas; ICD, 8th revision, 189.1) or kidney (adenocarcinomas; ICD 189.0), and sought evidence of 'intermediate' or 'advanced' RPN, according to Burry [8], without prior knowledge of the analgesic history. Cases were excluded if the presence or absence of RPN could not be established, because either the section submitted did not show papilla or the papillary architecture was obscured by the tumor. A history of analgesic consumption was obtained through completion of a structured questionnaire at interview [9] by MMcC or JHS, who at the time were unaware of the histopathological findings. So included were 66 cases of CaP (44 female, 22 male) and 86 cases of CaK (27 female, 59 male).

For the estimation of relative risk, data were included from a control group comprising 444 female (aged 45 to 84 yr) and 307 male (50 to 89 yr) respondents from a systematic random sample of the adult population of New South Wales, obtained by taking every thousandth name from the electoral rolls [10, 11].

The total amount consumed of phenacetin–containing analgesics was calculated using the frequency and duration of consumption recorded in the questionnaire, together with the

Received for publication May 17, 1985,
and in revised form December 3, 1985

Table 1. Risk ratios for renal cancer according to (a) regular consumption of phenacetin-containing analgesics (PhA) and (b) renal papillary necrosis (RPN)

	Cancer of the renal pelvis		Cancer of the renal parenchyma		Population controls[a]	
	F	M	F	M	F	M
N	44	22	27	59	444	307
Age *mean* ± SD	61 ± 9	62 ± 9	61 ± 13	61 ± 10	60 ± 9	62 ± 8
PhA +, RPN +[b]	23	4	1	0	31	4
PhA +, RPN −	5	2	3	10	22	22
PhA −, RPN +	2	1	0	1	9	2
PhA −, RPN −	14	15	23	48	382	279
Risk ratios[c]						
Associated with PhA						
−RPN absent	3.6 (1.6—8.1)[d]		2.5 (1.3—4.9)[d]			
−RPN present	20 (12—34)[d]		0.4 (0.1—2.7)			
Associated with RPN						
−PhA absent	6.9 (2.1—22)[d]		1.1 (0.1—9.6)			

[a] Population controls were distributed according to estimates of RPN in the Brisbane population (9% in women, 2% in men) [16, 17] and the relative risk for RPN associated with PhA of 27 [18]
[b] + = present; − = absent
[c] Mantel–Haenszel estimates (adjusted for sex) with 95% confidence limits
[d] 99% confidence limits also lay entirely above 1.0

known composition of various analgesic preparations. A lifetime total of at least 1 kg (that is, about four powders or tablets a day for one year of preparations containing aspirin, phenacetin and either caffeine or codeine) was considered to represent 'regular', and less than this amount 'never regular', consumption.

Statistical analysis

Relative risks (RR) were calculated according to the Mantel–Haenszel formula [12]:

$$RR = (a/b) / (c/d)$$

where a = number of cases exposed to the risk factor,
b = number of cases not exposed,
c = number of controls exposed,
d = number of controls not exposed.

For each of the two risk factors examined, stratification was employed to take into account the presence or absence of the other, and the sex of the subject. The relative risks together with Miettinen's test-based confidence limits [13] were computed as described by Breslow and Day [14] using calculator programs devised by Rothman and Boice [15].

Results

The age at diagnosis (for cases) or interview (for controls) was similar in the three groups (Table 1). The distribution of cases with renal pelvic (CaP) or parenchymal (CaK) cancer and population controls is given according to whether each had (a) renal papillary necrosis (RPN) and (b) taken phenacetin–containing analgesics (PhA) regularly.

From Table 1, it can be calculated that the prevalence of RPN among analgesic takers with CaP with 79% (27 out of 34) while the corresponding figure for CaK was 7% (1 out of 14). This difference could not readily be explained by the amount or duration of PhA consumption (Table 2).

Table 2. Consumption of phenacetin–containing analgesics by subjects with cancer of the renal pelvis or renal parenchyma

		Phenacetin–containing analgesics		
Cancer of the renal pelvis		No. of consumers	Amount consumed *kg*	Duration of consumption *yr*
RPN[a] − present	(*N* = 30)	27	24 ± 17	29 ± 16
− absent	(*N* = 36)	7	19 ± 17	22 ± 17
Cancer of the renal parenchyma				
RPN − present	(*N* = 2)	1	27	24
− absent	(*N* = 84)	13	13 ± 14	21 ± 14
Controls				
	(*N* = 751)	79	14 ± 19	16 ± 11

[a] RPN = renal papillary necrosis

As it was not possible to determine directly whether or not RPN was present in the population controls, this group was partitioned (Table 1) according to (i) PhA consumption as recorded in the questionnaire, (ii) a prevalence of RPN for the whole control group of 9% for women, and 2% for men, as determined from two Brisbane autopsy surveys [16, 17] and (iii) a relative risk for RPN of 27 in those who had consumed at least 1 kg of PhA when compared with those consuming less than this amount. This relative risk of 27 was calculated for the New South Wales population from data previously published [18], but reanalyzed using the level of analgesic consumption set for this study.

In the absence of the other risk factor, RPN increased the relative risk for CaP some sevenfold while PhA consumption increased the risk by a factor of about 3-1/2. When both were present, however, the risk was increased to 20 times that for persons exposed to neither risk factor (Table 1).

The relative risk for CaK was doubled by the consumption of PhA, but was not increased by the presence of RPN. Indeed, as the prevalence of RPN among cases with CaK was less than that estimated for the control group, the presence of RPN

appeared to decrease the risk for analgesic–associated CaK (Table 1).

Discussion

In order to calculate risk ratios for cancer of the kidney associated with the presence of renal papillary necrosis (RPN), the frequency of RPN must be known in the control group as well as in the cancer groups. Because the diagnosis of RPN can be made only by pathological examination of the kidney or, less certainly, by pyelography, neither of which could be contemplated in the population control group, we were obliged to use an indirect estimate of the occurrence of RPN in these subjects. The only autopsy surveys performed in Sydney have been in patients dying in teaching hospitals [19, 20], a category known to have a higher prevalence of RPN than the population–at–large [16, 17]. Therefore, we have used figures relating to two series of coroner's autopsies in another large Australian city, Brisbane [16, 17]. This was felt to be justified as the frequencies of RPN in the hospital autopsy studies in Brisbane and Sydney were similar and the Brisbane population has consumed phenacetin–containing analgesics (PhA) at about the same rate as Sydney residents [21, 22]. The female:male ratios of 4.5:1 in the prevalence of RPN in the Brisbane coroner's surveys accords with that of two series of Sydney cases of RPN (5:1 [23]; 7:1 [18]).

Given that this estimate of the prevalence of RPN in the population is accurate, our results indicate that both RPN and regular PhA consumption are independent risk factors for renal pelvic cancer (CaP), increasing the risk by a factor of about 7 and 3-1/2 respectively.

Were the Brisbane figures to be an overestimate of the prevalence of RPN in the NSW population, as suggested by the frequency of RPN in our cases with CaK (4% in women, 2% in men), the case for RPN having a carcinogenic role in the development of CaP would be strengthened. However, as the median age of the Brisbane cases lies between 55 and 60 in both sexes (that is, about five years younger than in our patients) then, because the frequency of RPN increases with age, the prevalence that we have used may be an underestimate. Because of this, we have calculated what the relative risk would be were the true prevalence in the population–at–large 1-1/2 times that used for the calculations given in Table 1. The relative risks then would be 5 for RPN alone, 6 for PhA consumption alone and 13 for the presence of both factors together.

All our cancer cases were from large teaching hospitals to which cases with RPN may have been preferentially referred because of associated urinary obstruction or infection, renal failure, or hypertension. While this may have been a source of selection bias, the proportion of analgesic–associated pelvic tumors found with coexisting RPN in this series, 79%, is within the range recorded in previously published studies [4–7].

If the nephrotoxic and carcinogenic effects of phenacetin–containing analgesics occurred separately, the risk for CaP associated with PhA consumption would be unaltered by the presence or absence of RPN. Clearly the data examined here deny this possibility, for the risk among patients exposed to PhA was more than five times greater in the presence of RPN than in its absence. Indeed, the Mantel–Haenszel risk ratios (stratified for sex) indicated that RPN and PhA consumption each had non-chance associations with CaP in the absence of the other factor; and, when both factors were present, the risk increased in a multiplicative fashion. This suggests that PhA and RPN have independent, and when they coexist sequential, effects.

Could the presence of RPN in cancer–bearing kidneys merely reflect the fact that in the course of evolution of PhA-induced renal disease, the nephrotoxic effect (RPN) appears before the carcinogenic effect (CaP)? Certainly RPN is more common than CaP, but in previous investigations [9–11, 18], there was no difference in either the quantity, or the duration of PhA consumption leading to each of the two diseases. Moreover, the data in Table 2 show that the amount of PhA consumed by the cancer patients was only moderately (and not significantly) higher in those with RPN than in those without. It is also clear from this table that RPN is by no means an invariable consequence of heavy PhA consumption. Given the present observations and those already published, it does appear that there is a closer association between RPN and CaP than can be explained purely on the basis of the two diseases being caused by heavy exposure to the same agent.

Previous studies have shown that CaP and RPN are both associated with analgesics that contain phenacetin (mainly powders or tablets of aspirin, phenacetin and caffeine or codeine) but not with those which contain no phenacetin (mainly aspirin and/or paracetamol with or without other ingredients) [9–11]. An examination of the primary data from the case–control studies reported in references 9 to 11 and 18 showed no association of paracetamol–containing analgesic consumption with cancer of the kidney or renal pelvis or with RPN, when the effect of exposure to phenacetin was taken into account in the calculation. Moreover, there is no experimental evidence implicating paracetamol with cancer at these sites. Phenacetin's carcinogenic effect is thought to result from the potent alkylating action of the N-O-sulphate and -glucuronide conjugates of N-hydroxy-phenacetin [24]. However, the chief metabolite of phenacetin, paracetomol, probably does not undergo N-hydroxlation [25].

That regular PhA consumption appears to double the risk for cancer of the kidney (CaK) in this series is in keeping with the findings of a case–control study from Minneapolis, which demonstrated a relative risk for CaK of 2.2 for men and 2.5 for women associated with prolonged use of this type of analgesic [26]. However, unlike the situation in CaP, there is no body of clinical evidence linking RPN with CaK, nor did our results suggest that such an association was likely. Thus, the relationship between consumption of phenacetin–containing analgesics and CaK appears to be entirely a direct one without any intervening effect of RPN.

Acknowledgments

This study was supported by the New South Wales State Cancer Council and the National Health and Medical Research Council of Australia. The participating hospitals were Sydney, Prince Henry, Concord, St. Vincent's, Royal North Shore and Westmead.

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